Major Spanish contributions to our current understanding of pneumococcal biology

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1. Introduction

Since its discovery at the end of the 19th century [1, 2], the pneumococcus has been recognized as a leading human pathogen, especially in children and the elderly. This fastidious microorganism has been the subject of thousands of research papers over the years. A search of the PubMed database (NCBI) for "*Streptococcus pneumoniae*" returned over 24,000 papers published between 1971 and 2012. Half of them were published in the last 12 years (Fig. 1), coinciding with the global spread of antibiotic-resistant pneumococci, a problem that led to increased funding for research into this bacterium. A plateau now appears to have been reached with ca. 1000 papers published every year.

Around 1990, the prevalence of antibiotic-resistant *S. pneumoniae* strains was reported to be ≤5% in the USA and most European countries. In contrast, up to 65% of pneumococci were reported resistant to one or more antibiotics in Spain [3]. For years, the situation in Spain has been thought of as a sign of things to come in pneumococcal epidemiology, largely due to the skillful work of J. Casal and A. Fenoll and their group at the Spanish Pneumococcal Reference Centre.

2. Early times

Most of the early studies on the biology of pneumococcus were performed in USA and Germany [4]. Some research was, however, undertaken in Spain. In 1934, studies were performed in nasopharyngeal carriers of pneumococcus [5], and somewhat surprisingly were continued (at least to some extent) after the Spanish Civil War [6]. Although the first capsular typings made use of sera kindly provided by German scientists, specific anticapsular sera would later be developed at the Instituto de Biología y Sueroterapia (IBYS) founded in 1919 in Madrid [7, 8].

3. Modern times of pneumococcal research in Spain

The PubMed and Scopus databases were also searched for studies (published in English and appearing in peer-reviewed journals) undertaken by Spanish research groups or international groups with large Spanish participation. Only those publications in which *S. pneumoniae* was the main subject were taken into account. Since the time of the first paper that met the search requirements [9], nearly a thousand more have been published. Figure 1 shows an apparent growing trend with respect to Spanish publications in this area. Many research fields were covered by the detected papers, which, grosso modo, can be defined as: 1) molecular biology and virulence, 2) mobile elements –including plasmid and phage biology, 3) diagnosis, 4) antibiotic resistance, 5) epidemiology, and 6) pneumococcal vaccination.

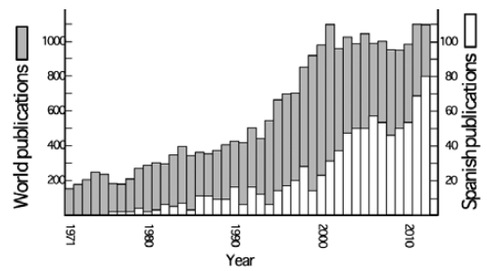

Fig. 1: World and Spanish publications on pneumococcus between 1971 and 2012.

Although the first of these publications were produced by researchers in Madrid and Barcelona,

a growing number of groups (many in Spain's National Health System hospitals) in other cities would begin to publish. Researchers from all over the country are now represented.

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Molecular insights that link chromosome biology with competence development in *Streptococcus pneumoniae*

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Competence is a tightly regulated physiological state in which bacteria become able to take up exogenous DNA and use it for genetic transformation. In the human pathogen *Streptococcus pneumoniae*, treatment by certain antibiotics has been shown to trigger competence and might thus accelerate the occurrence of multidrug resistance and promote the evolution of virulence (Prudhomme et al., 2006, *Science*). How competence is induced by antibiotics however, remains poorly understood. We recently showed that *S. pneumoniae* contains a functional chromosome segregation machine by binding of the conserved DNA-binding protein ParB to centromere-like DNA sequences (*parS*) located near the origin of replication *(oriC*) (Minnen et al., 2011, *Mol. Microbiol*.). *ParB*/*parS* complexes promote chromosome segregation, probably by recruiting the Structural Maintenance of Chromosomes complex (SMC) to *oriC*. Intriguingly, all the operons implicated in the development of natural competence (*i.e. comCDE, comAB and comX*) are also located near oriC. In this presentation I will discuss how ParB regulates competence by binding to, and spreading from, a parS site at 10 kb from oriC into the nearby *comCDE* operon. In addition, I will present data that explains why certain antibiotics that target chromosome biology induce competence, and in fact activate stress responses in many bacteria by a general mechanism.